Potassium Chloride Extended-Release Capsules

<table>
<thead>
<tr>
<th>Type of Posting</th>
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<td>Posting Date</td>
<td>18-Dec-2020</td>
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<td>Official Date</td>
<td>1-Jan-2021</td>
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<td>Expert Committee</td>
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In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 5 Expert Committee has revised the Potassium Chloride Extended-Release Capsules monograph. The purpose for the revision is to add *Dissolution Test 4* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution tests.

- *Dissolution Test 4* was validated using a Dionex Ion Pac CS12A-Analytical brand of column with L106 packing. The typical retention time for potassium is about 5.6 min.

The Potassium Chloride Extended-Release Capsules Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Josan Thomas, Scientific Liaison (+91-4044488948 or josan.thomas@usp.org).
Potassium Chloride Extended-Release Capsules

**DEFINITION**
Potassium Chloride Extended-Release Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of potassium chloride (KCl).

**IDENTIFICATION**

- **A. IDENTIFICATION TESTS—GENERAL (191), Chemical Identification Tests, Potassium**
  - **Sample solution:** A portion of the filtrate, obtained as directed for *Sample stock solution* in the Assay
  - **Acceptance criteria:** Meet the requirements

- **B. IDENTIFICATION TESTS—GENERAL (191), Chemical Identification Tests, Chloride**
  - **Sample solution:** A portion of the filtrate, obtained as directed for *Sample stock solution* in the Assay
  - **Acceptance criteria:** Meet the requirements

**ASSAY**

- **Procedure**
  - **Standard stock solution:** 19.07 μg/mL of potassium chloride, previously dried at 105° for 2 h, in water. This solution contains 10 μg/mL of potassium.
  - **Standard solutions:** To separate 100-mL volumetric flasks transfer 10.0, 15.0, and 20.0 mL, respectively, of *Standard stock solution*. To each flask add 2.0 mL of sodium chloride solution (200 mg/mL) and 1.0 mL of hydrochloric acid, and dilute with water to volume. The *Standard solutions* contain, respectively, 1.0, 1.5, and 2.0 μg/mL of potassium.
  - **Sample stock solution:** Place NLT 20 Capsules in a suitable container with 400 mL of water, heat to boiling, and boil for 20 min. Allow to cool, transfer the solution to a 1000-mL volumetric flask, and dilute with water to volume. Filter, discarding the first 20 mL of the filtrate. Transfer a measured volume of the subsequent filtrate, equivalent to 60 mg of potassium chloride, to a 1000-mL volumetric flask, and dilute with water to volume. [Note—Retain a portion of the filtrate for use in the *Identification* tests.]
  - **Sample solution:** Transfer 5.0 mL of *Sample stock solution* to a 100-mL volumetric flask. Add 2.0 mL of sodium chloride solution (200 mg/mL) and 1.0 mL of hydrochloric acid, and dilute with water to volume.

**Instrumental conditions**

(See *Atomic Absorption Spectroscopy* (852).)

- **Mode:** Atomic absorption spectrophotometry
- **Analytical wavelength:** Potassium emission line at 766.5 nm
- **Lamp:** Potassium hollow-cathode
- **Flame:** Air–acetylene
- **Blank:** Water

**Analysis**

- **Samples:** Standard solutions, Sample solution, and Blank
  - Plot the absorbance of the *Standard solutions* versus the concentration of potassium, in μg/mL, and draw the straight line best fitting the three plotted points. From the graph, determine the concentration of potassium in the *Sample solution* (μg/mL).
  - Calculate the percentage of the labeled amount of potassium chloride (KCl) in each Capsule taken:

\[
\text{Result} = \left( \frac{C}{C_U} \right) \times \left( \frac{M}{A_p} \right) \times 100
\]

- \( C \) = concentration of potassium in the *Sample solution* as determined in this test (μg/mL)
- \( C_U \) = concentration of potassium chloride in the *Sample solution* (μg/mL)
\( M_r \) = molecular weight of potassium chloride, 74.55

\( A_r \) = atomic weight of potassium, 39.10

Acceptance criteria: 90.0\%–110.0\%

PERFORMANCE TESTS

Change to read:

- **Dissolution** (711)

Test 1

**Medium**: Water; 900 mL

**Apparatus 1**: 100 rpm

**Time**: 2 h

**Standard stock solution**: 19.07 µg/mL of potassium chloride, previously dried at 105\(^\circ\)C for 2 h, in water. This solution contains 10 µg/mL of potassium.

**Standard solutions**: To separate 100-mL volumetric flasks transfer 10.0, 15.0, and 20.0 mL, respectively, of Standard stock solution. To each flask add 2.0 mL of sodium chloride solution (200 mg/mL) and 1.0 mL of hydrochloric acid, and dilute with water to volume. The Standard solutions contain, respectively, 1.0, 1.5, and 2.0 µg/mL of potassium.

**Sample stock solution**: Filter the solution under test, and dilute quantitatively with Medium to obtain a solution containing 60 µg/mL of potassium chloride.

**Sample solution**: Add 5.0 mL of the Sample stock solution to a 100-mL volumetric flask, add 2.0 mL of sodium chloride solution (200 mg/mL) and 1.0 mL of hydrochloric acid, and dilute with water to volume.

**Instrumental conditions**

(See **Atomic Absorption Spectroscopy (852)**.)

**Mode**: Atomic absorption spectrophotometry

**Analytical wavelength**: Potassium emission line at 766.5 nm

**Lamp**: Potassium hollow-cathode

**Flame**: Air–acetylene

**Blank**: Water

**Analysis**

**Samples**: Standard solutions, Sample solution, and Blank

Plot the absorbance of the Standard solutions versus the concentration of potassium, in µg/mL, and draw the straight line best fitting the three plotted points. From the graph, determine the concentration of potassium in the Sample solution (µg/mL).

Calculate the percentage of the labeled amount of potassium chloride (KCl) dissolved:

\[
\text{Result} = \left[ C \times D \times \left( \frac{V}{L} \right) \right] \times \left( \frac{M_r}{A_r} \right) \times 100
\]

- \( C \) = concentration of potassium in the Sample solution as determined in this test (µg/mL)
- \( D \) = dilution factor of the Sample solution
- \( V \) = volume of Medium, 900 mL
- \( L \) = labeled amount of potassium chloride (µg/Capsule)
- \( M_r \) = molecular weight of potassium chloride, 74.55
- \( A_r \) = atomic weight of potassium, 39.10

**Tolerances**: NMT 35\% (Q) of the labeled amount of potassium chloride (KCl) is dissolved in 2 h. The requirements are met if the quantities dissolved from the Capsules tested conform to **Table 1** instead of to the table shown in Dissolution (711).
**Table 1**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number Tested</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_1$</td>
<td>6</td>
<td>Each unit is within the range $Q \pm 30%$.</td>
</tr>
<tr>
<td>$S_2$</td>
<td>6</td>
<td>Average of 12 units ($S_1 + S_2$) is within the range between $Q - 30%$ and $Q + 35%$, and no unit is outside the range $Q \pm 40%$.</td>
</tr>
<tr>
<td>$S_3$</td>
<td>12</td>
<td>Average of 24 units ($S_1 + S_2 + S_3$) is within the range between $Q - 30%$ and $Q + 35%$, and NMT 2 units are outside the range $Q \pm 40%$.</td>
</tr>
</tbody>
</table>

**Test 2:** If the product complies with this procedure, the labeling indicates that it meets USP Dissolution Test 2.

**Standard stock solution** and **Standard solutions:** Prepare as directed in Test 1.

**Medium:** Water; 900 mL

**Apparatus 1:** 100 rpm

**Times:** 1, 2, 4, and 6 h

**Sample stock solution:** Transfer 4.0 mL of the solution under test into a 50-mL volumetric flask, dilute with water to volume, and filter.

**Sample solution:** Transfer 4.0 mL of the Sample stock solution to a 100-mL volumetric flask. Add 2.0 mL of sodium chloride solution (200 mg/mL) and 1.0 mL of hydrochloric acid, and dilute with water to volume.

**Blank solution:** To a 100-mL volumetric flask, add 2.0 mL of sodium chloride solution (200 mg/mL) and 1.0 mL of hydrochloric acid, and dilute with water to volume.

**Instrumental conditions:** Proceed as directed in Test 1, except do not use the Blank.

**System suitability**

**Samples:** Standard solutions

**Suitability requirements**

**Linearity:** Correlation coefficient NLT 0.99

**Relative standard deviation:** NMT 5.0% from 5 replicate analyses of the 1.5-µg/mL Standard solution

**Analysis**

**Samples:** 1.5-µg/mL Standard solution, Sample solution, and Blank solution

Calculate the percentage of the labeled amount of potassium chloride (KCl) dissolved:

\[
\text{Result}_i = \left[ \frac{(A_U/A_S) \times C_S \times D \times (V/L) \times (M_r/A_p)}{\times 100} \right]
\]

$A_U$ = absorbance of potassium in the Sample solution

$A_S$ = absorbance of potassium in the Standard solution

$C_S$ = concentration of potassium in the Standard solution (µg/mL)

$D$ = dilution factor of the Sample solution

$V$ = volume of Medium, 900 mL

$L$ = labeled amount of potassium chloride (µg/Capsule)

$M_r$ = molecular weight of potassium chloride, 74.55
\[ A_r \] = atomic weight of potassium, 39.10

**Tolerances:** See *Table 2.*

**Table 2**

<table>
<thead>
<tr>
<th>Time Point (( I ))</th>
<th>Time (h)</th>
<th>Amount Dissolved (%) 750 mg/Capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>25–45</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>45–65</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>70–90</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of potassium chloride (KCl), dissolved at the times specified, conform to *Dissolution (711), Acceptance Table 2.*

**Test 4:** If the product complies with this procedure, the labeling indicates that it meets USP Dissolution Test 4.

[NOTE—Use water with a conductivity of NMT 1 \( \mu \text{S/cm} \) to prepare solutions, except Medium.]

**Medium:** Water; 900 mL

**Apparatus 1:** 100 rpm

**Times:** 1, 2, 4, and 8 h

**Solution A:** 100 mM methanesulfonic acid prepared as follows. Transfer 6.5 mL of methanesulfonic acid to a 1000-mL volumetric flask and dilute with water to volume.

**Mobile phase:** Solution A and water (20:80)

**Standard stock solution:** 600 \( \mu \text{g/mL} \) of *USP Potassium Chloride RS* in water

**Standard solution A:** 3 \( \mu \text{g/mL} \) of *USP Potassium Chloride RS* in water from Standard stock solution

**Standard solution B:** 12 \( \mu \text{g/mL} \) of *USP Potassium Chloride RS* in water from Standard stock solution

**Standard solution C:** 30 \( \mu \text{g/mL} \) of *USP Potassium Chloride RS* in water from Standard stock solution

**Standard solution D:** 48 \( \mu \text{g/mL} \) of *USP Potassium Chloride RS* in water from Standard stock solution

**Standard solution E:** 60 \( \mu \text{g/mL} \) of *USP Potassium Chloride RS* in water from Standard stock solution

**Standard solution F:** 72 \( \mu \text{g/mL} \) of *USP Potassium Chloride RS* in water from Standard stock solution

**Standard solution G:** 90 \( \mu \text{g/mL} \) of *USP Potassium Chloride RS* in water from Standard stock solution

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-\( \mu \text{m} \) pore size at the times specified, discarding the first few milliliters of the filtrate. Replace the portion removed with same volume of Medium. Dilute the filtrate with water, if necessary, to obtain a solution with a concentration similar to that of Standard solution E.

**Chromatographic system**

(See *Chromatography (621), System Suitability.*)

**Mode:** LC

**Detector:** Conductivity with suppression

**Columns**

- **Guard:** 4-mm \( \times \) 5-cm; 8.5-\( \mu \text{m} \) packing L106
- **Analytical:** 4-mm \( \times \) 25-cm; 8.5-\( \mu \text{m} \) packing L106

**Suppressor:** 4-mm cation or a suitable suppressor

**Column temperature:** 30\(^\circ\)

**Flow rate:** 1 mL/min

**Injection volume:** 50 \( \mu \text{L} \)
Run time: NLT 2.5 times the retention time of potassium

System suitability


Suitability requirements

Tailing factor: NMT 2.0, Standard solution E
Relative standard deviation: NMT 2.0%, Standard solution E
Correlation coefficient: NLT 0.999, from the linear regression in the Analysis
Y-intercept: ±2% of Standard solution E response, from the calibration curve in the Analysis

Analysis


From the linear calibration curve, determine the Correlation coefficient and Y-intercept.

Calculate the concentration ($C_i$) of potassium chloride (KCl) in the sample withdrawn from the vessel at time point $i$:

$$\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times D$$

$r_U$ = peak response of potassium from the Sample solution at time point $i$

$r_S$ = peak response of potassium from Standard solution E

$C_S$ = concentration of USP Potassium Chloride RS in Standard solution E (mg/mL)

$D$ = dilution factor of the Sample solution, if needed

Calculate the percentage of the labeled amount of potassium chloride (KCl) dissolved at each time point ($i$):

$$\text{Result}_1 = C_1 \times V \times \left( \frac{1}{L} \right) \times 100$$

$$\text{Result}_2 = \left[ (C_2 \times V) + (C_1 \times V_S) \right] \times \left( \frac{1}{L} \right) \times 100$$

$$\text{Result}_3 = \left[ (C_3 \times V) + (C_2 + C_1) \times V_S \right] \times \left( \frac{1}{L} \right) \times 100$$

$$\text{Result}_4 = \left[ (C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S] \right] \times \left( \frac{1}{L} \right) \times 100$$

$C_i$ = concentration of potassium chloride in the portion of sample withdrawn at time point $i$ (mg/mL)

$V$ = volume of Medium, 900 mL

$L$ = label claim (mg/capsule)

$V_S$ = volume of the Sample solution withdrawn at each time point (mL)

Tolerances: See Table 3.

Table 3
<table>
<thead>
<tr>
<th>Time Point ((i))</th>
<th>Time ((h))</th>
<th>Amount Dissolved ((%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>NMT 20</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>25–45</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>55–80</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentage of the labeled amount of potassium chloride (KCl) dissolved at the times specified conforms to *Dissolution (711)*, *Acceptance Table 2*.\(^*\) (RB 1-Jan-2021)

*Uniformity of Dosage Units (905)*: Meet the requirements

**ADDITIONAL REQUIREMENTS**

*Packaging and Storage*: Preserve in tight containers, and store at a temperature not exceeding 30°.

*Labeling*: When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.

**Add the following:**

\(^*\) *USP Reference Standards (11)*

*USP Potassium Chloride RS*\(^*\) (RB 1-Jan-2021)

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**Page Information:**

Not Applicable

**DocID:**

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